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10/560,737	12/15/2005	Timo Heinrich	Merck-3100	1689

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
JARRELL, NOBLE E	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
10/01/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,737	HEINRICH ET AL.	
	Examiner	Art Unit	
	NOBLE JARRELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,12,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,12,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. In the current application, claims 1, 2, 3, 4, 6, 7, 8, 9, 12, 14, and 15 are pending.

2. After review of the final rejection with SPRE Marianne Seidel, it was agreed that this case should be reopened. Consequently, a non-final action is being done.

3. The rejection under obvious-type double patenting regarding 10/481270 has been dropped because the patented claims are drawn to a process of making a compound that is not overlapping with the claims of the instant application.

4. The 35 U.S.C. rejection 112 1st paragraph regarding solvates for claims 1-4, 6-9, and 12 has been overcome. However it remains for claim 15 as set forth below.

5. The 35 U.S.C. 112 1st paragraph rejection regarding the *in vitro* treatment has been overcome because premenstrual syndrome is not embraced by method claims 12 and 15. According to the medical subject heading (see 35 U.S.C. 112 2nd paragraph rejection for claim 12), premenstrual syndrome is not a psychological or physiological sexual dysfunction.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the achievement of an anxiolytic or antidepressant effect and the treatment of obsessive-compulsive disorder with a 5-HT_{1A} agonist and the achievement of an anxiolytic or antidepressant effect and the treatment of obsessive-compulsive disorder, or anorexia with a selective serotonin reuptake inhibitor, does not reasonably provide enablement for the remaining uses covered. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and predictability in the art:

The claims are drawn to "positively influencing" through agonism of 5-HT_1 or selective serotonin reuptake inhibition by using compounds described by an indol-3-yl-C_{2-6}-alkyl-(piperazine or piperidine)-C_{0-4}-alkyl-benzofuran structure. The invention is directed toward medicine and is therefore physiological in nature. It is well-established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher* (166 USPQ 18,24 (CCPA 1970).

(2) The breadth of the claims

The extremely diverse range of sleep disorders covers Dyssomnias, Parasomnias, Medical/Psychiatric Sleep Disorders and others. First there are the Intrinsic Sleep Disorders, including Psychophysiological Insomnia, Sleep State Misperception, Idiopathic Insomnia, Narcolepsy, Recurrent Hypersomnia, Idiopathic Hypersomnia, Posttraumatic Hypersomnia, Obstructive Sleep Apnea Syndrome, Central Sleep Apnea Syndrome, Central Alveolar Hypoventilation Syndrome, Periodic Limb Movement

Disorder, Restless Legs Syndrome, and Intrinsic Sleep Disorder NOS. Second there are the Extrinsic Sleep Disorders, including Inadequate Sleep Hygiene, Environmental Sleep Disorder, Altitude Insomnia, Adjustment Sleep Disorder, Insufficient Sleep Syndrome, Limit-Setting Sleep Disorder, Sleep-Onset Association Disorder, Food Allergy Insomnia, Nocturnal Eating (Drinking) Syndrome, Hypnotic-Dependent Sleep Disorder, Stimulant-Dependent Sleep Disorder, Alcohol-Dependent Sleep Disorder, Toxin-Induced Sleep Disorder, and Extrinsic Sleep Disorder NOS. Third, there are Circadian Rhythm Sleep Disorders, including Time Zone Change (Jet Lag) Syndrome, Shift Work Sleep Disorder, Irregular Sleep-Wake Pattern, Delayed Sleep Phase Syndrome, Advanced Sleep Phase Syndrome, Non-24-Hour Sleep-Wake Disorder, and Circadian Rhythm Sleep Disorder NOS. Fourth, there are Arousal Disorders, including Confusional Arousals, Sleepwalking, and Sleep Terrors. Fifth, there are Sleep-Wake Transition Disorders, including Rhythmic Movement Disorder, Sleep Starts, Sleep Talking, and Nocturnal Leg Cramps. Sixth, there are Parasomnias Usually Associated with REM Sleep, including, Nightmares, Sleep Paralysis, Impaired Sleep-Related Penile Erections, Sleep-Related Painful Erections, REM Sleep Related Sinus Arrest, and REM Sleep Behavior Disorder. Seventh, there are Other Parasomnias, including Sleep Bruxism, Sleep Enuresis, Sleep-Related Abnormal Swallowing Syndrome, Nocturnal Paroxysmal Dystonia, Sudden Unexplained Nocturnal Death Syndrome, Primary Snoring, Infant Sleep Apnea, Congenital Central Hypoventilation Syndrome, Sudden Infant Death Syndrome, Benign Neonatal Sleep Myoclonus, and Other Parasomnia NOS. Eighth, there are Sleep Disorders Associated with Mental Disorders, including Psychoses, Mood Disorders, Anxiety Disorders, Panic Disorder and Alcoholism. Ninth, there are Sleep Disorders Associated with Neurological Disorders, including, Cerebral

Degenerative Disorders, Dementia, Parkinsonism, Fatal Familial Insomnia, Sleep-Related Epilepsy, Electrical Status Epilepticus of Sleep, and Sleep-Related Headaches. Tenth, there are Sleep Disorders Associated with Other Medical Disorders, including, Sleeping Sickness, Nocturnal Cardiac Ischemia, Chronic Obstructive Pulmonary Disease, Sleep-Related Asthma, Sleep-Related Gastroesophageal Reflux, Peptic Ulcer Disease and Fibrositis Syndrome. In addition, there are an assortment of poorly defined disorders and syndromes, including Short Sleeper, Long Sleeper, Subwakefulness Syndrome, Fragmentary Myoclonus, Sleep Hyperhidrosis, Menstrual-Associated Sleep Disorder, Pregnancy-Associated Sleep Disorder, Terrifying Hypnagogic Hallucinations, Sleep-Related Neurogenic Tachypnea, Sleep-Related Laryngospasm, and Sleep Choking Syndrome.

Memory is the capacity to retain and retrieve an impression of past experiences. Memory is thus inseparable from learning, as learning cannot take place without memory and memory is the expression of learning.

Memory can be classified in two ways. One is, approximately, by duration. The sensory memory (milliseconds to seconds) corresponds to the initial moment that an item is perceived by the sense. Some of this information in the sensory area is transferred to short-term memory (retention for seconds to minutes). The capacity of these memories is quite limited. Some of this information is consolidated into long-term memory (retention for days up to a lifetime). The capacity of long term memory is immense. There is also something called working memory, which refers to a short-term storage needed for certain mental tasks but is not specifically defined in terms of duration, but rather in terms of purpose. It appears to be a form of short-term memory combined with some attentional control.

In addition, long term memory (the most important type) can be classified according to the information type. The two main categories are declarative (explicit) and non-declarative (implicit) memories. Declarative memory requires conscious recall, in that some conscious process must explicitly call back the information. This includes semantic memory, which concerns facts taken independent of context (mostly, general knowledge about the world); and episodic memory, which concerns information specific to a particular context, such as a time and place (mostly, personal memories and personal associations of a particular place or time, sometimes called autobiographical memory). The other main category's most important type is called procedural memory and is not based on the deliberate recall of information, but on an implicit learning of certain patterns about the world. This form of learning is responsible for improvements in performance due purely to repetition. Examples of this include Classical conditioning and motor learning (e.g. "muscle memory"), and many types of skills. The other type of non-declarative memory is perceptual-representational, a kind of "priming", so that the experience of an object on one occasion facilitates the perception of the same (or a similar) object on a later occasion.

Memory involves many different parts of the CNS, including basal ganglia, amygdala, the neostriatum, the cerebellum, the mammillary bodies and hippocampus.

The formation of memory requires three steps or stages: 1) Encoding (sensory registration, the processing of received information, including combination if the information comes from e.g. more than one sense organ), 2) Storage (creation of a permanent record of this encoded information), and 3) Retrieval (calling back this stored information in response to some cue for its use). As all of these are essential; a dysfunction of any stage will result in memory impairment. Thus, if the intial encoding

does not take place, or if this information is not transferred to short term memory, such as occurs in the various agnosias, then memory impairment will occur. If information cannot be moved from short term to long term memory (a disorder called anterograde amnesia), then memory impairment occurs. If retrieval from long term memory is delayed, if it cannot be performed (memories lost), or if it is defective (false memories), then there is memory impairment.

As a result of the wide range of different types of memories which the brain forms, and the great complexity of the processes for memory, this covers a very wide range of disorders.

These include language memory disorders, such as aphasias (e.g. conduction aphasia), apraxia, dysarthria, alexia, receptive dysphasia, and agraphia.

It includes many types of disorders called amnesias. There is anterograde amnesia (new events are not transferred to long-term memory) and retrograde amnesia (inability to recall events that occurred before the onset of amnesia). There is lacunar amnesia (loss of memory about one specific event), Fugue amnesia (Psychogenic amnesia or hysterical amnesia, including "repressed memories"), Childhood amnesia (inability to remember events from early childhood), Transient epileptic amnesia (TEA), Autobiographical Amnesia, Transient Global Amnesia (total memory loss), Source amnesia (in which someone can recall certain information, but not where or how it was obtained) and amnesias arising from complex partial seizures, and alcoholic blackouts.

It also includes various agnosias, such as Prosopagnosia, Integrative agnosias, asogmatoagnosia, Associative agnosias, Autotopagnosia , Time Agnosia, Apperceptive agnosia, object agnosia, finger agnosia, phonagnosia, central achromatopsia, topographical agnosia, dyslexia, dyscalculia, right-left disorientation, Optic ataxia and

Ocular apraxia, Color Agnosia, Simultanagnosia, Anosognosia, Auditory Agnosia (including amusia and word meaning deafness), and Somatosensory Agnosia (including Microsomatagnosia, Macrosomatagnosia, tactile agnosias and astereoagnosia), and constructional dyspraxia.

There is also Korsakoff's syndrome (Memory loss caused by alcoholism) and Post-traumatic stress disorder (spontaneous, vivid retrieval of unwanted traumatic memories), selective memory loss from head trauma, Accelerated Forgetting (excessively rapid decay of memories that appear to have been acquired successfully), and various types of false memory syndromes. There is the very common AAMI (age-associated memory impairment). Certain forms of Confusional States (e.g. those arising from latrogenic toxicity from some sedatives) will present acute memory disorders.

(3) The amount of direction or guidance presented:

That provided (page 17, line 18 to page 18, line 13) is limited. The dosage range is defective, in that it does not provide a daily dosage range, just that dosage depends on large number of individual factors. Moreover, this is generic, and the same applies to large number of disorders being treated. Thus, there is no specific guidance regarding a regimen or dosage effective against the disorders claimed.

Tests such as that presented in the specification (i.e. working example 3) are at best screening tests which alone are not usually indicative of clinical efficacy. See *Hoffman v. Klaus* 9 USPQ 2d 1657; *Ex parte Powers* 220 USPQ 924. Note also the criteria for enablement as set out in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition. Thus given the level of skill in this art which is low and the lack of direction (i.e. art-recognized tests) as well as working examples employing such tests, this rejection is being applied.

(4) The state of the prior art:

The test data presented in the specification is directed to testing for 5-HT_{1A} and 5-HT_4 binding affinity as stated on p. 22. While compounds having this activity are known to treat anxiety and depression, there are no such compounds known to treat any and all eating disorders and schizophrenia.

For schizophrenia alone, note Jones et al. (*Pharmacology, Biochemistry and Behavior*, **2002**, *71*, 555-568) provided by the examiner on p. 557, first sentence in "Schizophrenia" section states "...there is still much to be learned about the role of 5-HT..." and later that 5-HT_2 receptors (and not 5-HT_{1A}) may be implicated. Also see the section on "Cognitive disorders" on p. 562, especially the very first sentence. For sexual dysfunction, which entails all types of sexual disorders both male and female embraced by the claims section 17 in Jones mentions a very limited application for buspirone which is a 5-HT_{1A} partial agonist and 1 report for a 5-HT_3 receptor antagonist. SSRI's are also discussed. Due to their sexual side effects (delayed ejaculation in males) SSRI's are indicated for treating premature ejaculation.

Brown et al. (*Drug Discovery Today*, **2007**, *12 (17/18)*, pages 757-66), a more recent article directed to female sexual dysfunction (FSD) at best describes preliminary findings as can be seen in the discussion on p.763, right column, last paragraph in section entitled "5-HT_{1A} agonists".

Eglan et al. (*TiPS*, **1995**, *16*, 391-298) teach that the therapeutic potential of 5-HT_4 requires future research. Possible roles for the receptor appear possible; however more research is required ("Concluding Remarks", pages 396-7).

Spinks et al. (*Current Medicinal Chemistry*, **2002**, *9*, 799-810) teach that selective serotonin reuptake inhibitors (SSRI's) can be used as the following: antidepressants, anxiolytic compounds, compounds for the treatment of obsessive-compulsive disorder, and anorexia, (pages 799-800).

(5) The presence or absence of working examples:

There are none to treatment of any disorder. Working example 3 (page 22, lines 11 through 20) is of limited scope. It describes a compound of example 1 in which variable R^1 is 5-cyano, R^2 is methyl, m is four, Z is N, and R^3 is 2-$C(O)NH_2$, that has a nanomolar binding affinity to 5-HT_{1A} and 5-HT_4 receptors and a nanomolar reuptake inhibition of serotonin. Applicants provide a statement "Many of the compounds synthesized have nanomolar affinity to the 5-HT_{1A} receptors and nanomolar reuptake inhibition of serotonin." This statement is broad because it fails to define what other compounds prepared by applicants show nanomolar affinity or reuptake inhibition of serotonin.

(6) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position.

(8) The quantity of experimentation necessary:

In view of factors (1) through (6), this is extensive.

Considering the state of the art as discussed by the references above, particularly with regards to claim 12 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds and salts of formula I, does not reasonably provide enablement for solvates of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection over solvates was made in 1/23/2008 office action and is incorporated by reference.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is rejected because the phrase "an effective amount" is unclear because the intended use of the compound is not clear. An effective amount will change depending on what disorder is being treated. *In re Fredriksen and Nielsen* (102 USPQ 35) states the following: "the statement 'an effective amount' is in its face indefinite since it fails to state the function which is to be rendered effective. Therefore, the claim does not particularly point out the invention." In addition, what is the additional therapeutic agent in the kit? Applicants do not provide any guidance as to any specific agent (page 15, lines 13-16 and page 16, lines 16-20) that can be used in combination with a compound of formula I. The second agent is not limited to any use recited in the instant application, and consequently this agent is unclear for that reason as well.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1, 2, 3, 4, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bottcher et al. (US 5532241, published July 2, 1996, included in IDS).

Determining the scope and contents of the prior art

Bottcher describes compounds in examples 1, 2, 4, 5, 7, 8, 9, 10, and 11. In each of these compounds, variable R^2 is H.

In example 1, Bottcher describes compounds (column 9: lines 26-27; lines 49-50; lines 53-54) and column, lines 20-21) in which variable R^1 is 5-methoxy, 5-carboxyethyl, or 5-cyano; variable m is four; n is zero; and variable R^3 is 2-hydroxymethyl, a hydrogen substituent, or 2-carboxy. This compound is prepared by the reaction of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-hydroxymethylbenzofuran-5-yl)piperazine in 200 mL of acetonitrile (column 9, lines 16-28).

In example 2, a compound (column 10, lines 40-41) in which variable R^1 is CO_2H, m is four, n is zero, and R^3 is H, is described.

In example 4, a compound (column 11, lines 17-23) in which variable R^1 is 5-CN, m is four, n is zero, and R^3 is 2-carbamoyl, is described.

In example 5, compounds (column 5: lines 36-37, lines 45-46, lines 48-49, lines 51-52, lines 54-55, lines 58-59, and lines 61-62) are taught in which the following instances occur: variable R^1 is 5-cyano, 5-OH, 5-OMe, 5-CO_2Et, or 5-F; m is three, two, or four; n is zero; and variable R^3 is H.

In example 7, a compound (column 12, lines 50-51) in which variable R^1 is 5-CN, m is four, n is zero, and R^3 is C(O)NH-*t*-butyl, is described.

In example 8, compounds (column 13, lines 3-4, lines 13-14, lines 16-17, and lines 20-21) in which variable R^1 is 5-OH or 5-CH_2OH, m is four or two, n is zero, and variable R^3 is a hydrogen atom are described.

In example 9, compounds (column 13: lines 34-35, lines 39-40, lines 56-57, and lines 60-61; column 14: lines 9-10 and lines 14-15) are described in which variable R^1 is 5-CN, 5-OMe, 5-CO_2Et, or 5-CO_2Me; m is four, three or two; n is zero; and variable R^3 is 2-CO_2Et, 2-CN, 2-C(O)NHMe, or 2-CO_2H.

In example 10, a compound (column 14, lines 48-49) is described in which variable R^1 is 5-CH_2OH, m is four, n is zero, and R^3 is a H atom.

In example 11, a compound (column 15, lines 13-14) is described in which variable R^1 is 5-cyano, m is four, n is zero, and R^3 is 2-CO_2Me.

Bottcher teaches that a base of formula I can be converted into a corresponding acid addition salt (column 7, lines 31 to 49). Some examples of acids that can be used are sulfuric, hydrochloric, hydrobromic, orthophsphoric, and acetic acids, among others.

Bottcher teaches that described compounds can be used in pharmaceutical preparations (column 7, line 59 to column 8, line 23). The pharmaceutical preparation can be in form of a tablet, solution, ointment, cream, or powder. Examples A through H (column 15 line 17 to column 16, line 14) teach prepared formulations with compounds of formula I.

Bottcher teaches that compounds of formula I (which are prepared in the cited compounds of examples 1, 2, 4, 5, 7, 8, 9, 10, and 11) are active in terms of 5-HT_{1A} agonist and 5-HT reuptake inhibitors. The compounds are furthermore active as serotonin agonists and antagonists (column 1, lines 37 to 41). It is also stated that compounds of formula I of US 5532241 can be used as active ingredients for anxiolytics,

antidepressants, antipsychotics, neuroleptics, and/or hypertensives (column 1, lines 56 to 59). The prepared compounds can be used in the treatment of various diseases (column 8, lines 24 to 38). Some of these diseases are depression, psychoses, side-effects in the treatment of hypertension, acromegaly, hypogonadism, secondary amenorrhea, prementrual syndrome, undesired puerperal lactation, migraine headaches, and the control of sequelae of cerebral infarction (strokes and cerebral ischemia).

Ascertaining the differences between the prior art and the claims at issue

Bottcher describes compounds in which variable R^2 is a hydrogen atom. In amended claim 1, variable R^2 can be a methyl group among other groups.

Resolving the level of ordinary skill in the pertinent art

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of the elected group.

Considering objective evidence present in the application indicating obviousness or nonobviousness

In re Lohr and Spurlin (137 USPQ 548) teaches: When a new compound so closely related to a prior art compound as to be structurally obvious is sought to be patented based on the alleged greater effectiveness of the new compound for the same purpose as the old compound, clear and convincing evidence of substantially greater effectiveness is needed. Here there are no new properties, but merely an alleged improvement in the same property for use against the same pests.

In a comparison of the prior art and the pending claims of the instant application, the difference is the existence of NH group at the 1-position of an indole ring instead of a NMe group at the 1-position of the indole ring. Example 4 obviates compound a (lines 2-3) of claim 3. In compound a of claim 3, variable R^2 is methyl. The same compound (except for variable R^2) is described in compound a of claim 3 and the species described by Bottcher. In claim 3, the compounds are being described from the

benzofuran ring. In Bottcher, the compound is named from the piperazine ring. The cited compounds of Bottcher are being used for the same method of use as applicants. In fact, several of the effects are overlapping (anxiolytic, antidepressant, and neuroleptic) with the desired effects of claims 12 and 15 of application 10/560737. In the preparation of example 1, it is shown by Bottcher et al. that the presence of H vs. Me for variable R^2 is not critical for the coupling reaction between the piperazine reactant and the indole reactant. Due to the teachings of Bottcher et al., sufficient motivation to prepare and use the cited compounds exists. In addition, a reasonable expectation of success exists within the art exist because several methods of use are overlapping.

13. Claims 1, 2, 3, 6, 7, 8, 9, 12, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bathe et al. (WO 02/102794, published 27 December 2003, cited previously).

Determining the scope and contents of the prior art

Bathe describes a compound in which variable R_1 is 5-cyano, NR^2 is NH, m is four, X is N, n is zero, and R^3 is 2-$C(O)NH_2$ (lines 1-4 of the abtract).

Compositions involving this compound are taught on page 25, lines 10-19. The pharmaceutical forms that are taught are tablets as well as peroral and parenteral formulations. Compositions with another pharmaceutically active agent can be prepared (page 26, line 27 to page 27, line 2). Bathe cites a twin pack as one example (page 27, line 2). The composition can be a combined preparation for simultaneous, separate, or sequential use.

This compound can be used in the treatment of disorders (see abstract). These disorders are depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects of hypogonadism, secondary amenorrhea, premenstrual syndrome, and undesired puerperal lactation. Several of these disorders overlap with the

desired effects of claims 12 and 15 of application 10/560737: depressive disorders, anxiety disorders, sexual dysfunctions, eating disorders, obesity, and sleeping disorders.

Ascertaining the differences between the prior art and the claims at issue

Bathe describes a compound in which NR^2 is NH. In claims 1 and 2 of 10/560737, NR^2 can be NMe.

Resolving the level of ordinary skill in the pertinent art

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of the elected group.

Considering objective evidence present in the application indicating obviousness or nonobviousness

In re Lohr and Spurlin (137 USPQ 548) teaches: When a new compound so closely related to a prior art compound as to be structurally obvious is sought to be patented based on the alleged greater effectiveness of the new compound for the same purpose as the old compound, clear and convincing evidence of substantially greater effectiveness is needed. Here there are no new properties, but merely an alleged improvement in the same property for use against the same pests.

In the prior art, variable R^2 is H and in claim 1 of 10/560737, R^2 can be a methyl group. The species prepared by Bathe obviates compound a (lines 2-3) of claim 3. In compound a of claim 3, variable R^2 is methyl. The same compound (except for variable R^2) is described in compound a of claim 3 and the species described by Bathe. In claim 3, the compounds are being described from the benzofuran ring. In Bathe, the compound is named from the piperazine ring. *In re Lohr and Spurlin* teaches H vs. Me. is obvious in this art.

Bathe teaches that their compound can be used in the same method of use as is claimed in the instant application. Several of these disorders overlap with the desired effects of claims 12 and 15 of application 10/560737: depressive disorders, anxiety disorders, sexual dysfunctions, eating disorders, obesity, and

sleeping disorders. Based on these teachings, sufficient motivation exists to prepare this compound. A reasonable expectation of success also exists for the same reasons.

14. Claims 1, 2, 3, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartoszyk et al. (WO 02/39989, published 23 May 2002, cited previously).

Determining the scope and contents of the prior art

Bartoszyk teaches a compound (see 2nd line of abstract) where R_1 is 5-cyano, R^2 is H, m is four, X is N, n is zero, and R_3 is 2-$C(O)NH_2$ as a combined serotonin reuptake inhibitor and 5-HT_{1A} agonist. Compositions comprising this compound are taught on from page 8, line 16 to page 13, line 29. The forms of the compositions may be oral or peroral. Pharmaceutical products (examples A though I) are taught from page 21, line 6 to page 23, line 6).

The intended method of use for the cited compound is the treatment of pain (page 7, lines 10-13) or irritable bowel syndrome (page 11, line 24 to 31).

Ascertaining the differences between the prior art and the claims at issue

Bartoszyk teaches a compound in which NR^2 is NH. In claim 1 of 10/560737, NR^2 can be NMe.

Resolving the level of ordinary skill in the pertinent art

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of the elected group.

Considering objective evidence present in the application indicating obviousness or nonobviousness

Sterling Drug Inc. v. Watson, Comr. Pats. (108 USPQ 37) teaches that the test to be applied in the matter of the patentability of a compound that is a homologue of another is that the beneficial characteristics are both unexpected and obvious."

In a comparison of the prior art and the instant claims, the differences are the intended method use claimed and H vs. Me (for variable R^2 of 10/560737). The species prepared by Bartoszyk obviates compound a (lines 2-3) of claim 3. The same compound (except for variable R^2) is described in compound a of claim 3 and the species described by Bartoszyk. In compound a of claim 3, variable R^2 is methyl. In claim 3, the compounds are being described from the benzofuran ring. In Bartoszyk, the compound is named from the piperazine ring. *In re Lohr and Spurlin* teaches H vs. Me. is obvious in this art due to the following reasoning. Bartoszyk teaches that the cited compound works through the same receptor as compounds of the instant application (the 5-HT_{1A} receptor) and that it is also an agonist. In addition, the compound is a selective serotonin reuptake inhibitor. Therefore, whether variable R^3 is H or a methyl group is not critical to these compounds being effective. Based on the teachings of the case law and Bartoszyk et al., sufficient motivation to prepare this compound by itself and in various pharmaceutical preparations exists because it works through the same receptor.

Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624